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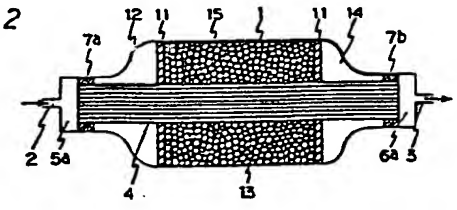
(54) **Apparatus for purifying blood.**

(57) An apparatus for purifying blood which is able to separate blood into plasma and blood rich in blood cells, to purify the separated plasma and to mix the purified plasma into the blood stream sumultaneously by itself. The apparatus comprises a hollow container (1) having a blood flow inlet (2) and a blood flow outlet (3) at the both ends thereof, respectively, an impure blood room (5a) and a purified blood room (6a) coupled with said inlet (2) and outlet (3), respectively, so that the blood can flow through them, a bundle of hollow fibers (4) made of semipermeable membrane connecting said impure blood room (5a) and said purified blood room (6a) so that the blood can flow through them, and a treating room (13) which is formed by dividing a space surrounded by said hollow container (1), impure blood room (5a) and purified blood room (6a) with porous partition plates (11) and said bundle of hollow fibers (4), and charged with a plasma treating agent (15).

FIG. 2



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APPARATUS FOR PURIFYING BLOOD

The present invention relates to an apparatus for purification of blood having a simple structure and capable for separation, purification and mixing of blood.

In recent years, a process for purifying blood, in which blood is separated into plasma and blood cells, the plasma is purified, and then, the purified plasma is mixed with the blood cells again, has been broadly employed. The process has an advantage that various biogenic rejections can be avoided since only objects to be eliminated is taken out from a patient body, and is free from a problem of a loss of the blood cells since only plasma is subjected to a purification.

As a method for separating the blood into plasma and blood cells, there are used, for instance, a centrifugation method, a membrane-employing method using a semipermeable hollow fiber or a porous membrane, and the like. For a method for purifying plasma, there is toward a practical use, an adsorbent system employing activated carbon, immunological adsorbent, and the like. Recently, a purifying agent utilizing an enzyme is also proposed.

When the above-mentioned process for purifying blood is carried out, it is necessary to adjust three processes to a most suitable condition, respectively, at all times; i.e. a process of separating plasma from blood, a process of purifying plasma and a process of mixing the purified plasma into the blood having a high concentration of blood cells.

Special care should be paid to the separating process of plasma from blood cells. If an excess pressure or mechanical force is gained to the blood at

the time of separation, the blood cells are destructed to cause a defunctionalization of blood. For preventing such a phenomenon, the membrane-employing method is desirably applied. But also in such a method, it is necessary to keep a trans membrane pressure within a definite range at all times, and a provision of the condition is complicated and troublesome. That is, to keep a trans membrane pressure within a definite range, it is necessary to control both a filtration pressure in the blood side and a pressure in the plasma side. Conventionally, two pumps have been employed and operated with suitable care, i.e. a pump for circulating the blood outside a body and a pump for controlling a taking speed of plasma.

Moreover, in a conventional apparatus, a plasma separator and a plasma purifying system must be arranged so that an additional connecting path between them should be provided owing to the above-mentioned requirement for controlling the separating process, and the apparatus becomes complicated.

For the purpose of solving many problems as described above, the present inventor have studied earnestly and have found a surprising fact, which is explained hereinafter referring to Fig. 1.

Fig. 1 is a schematic longitudinal sectional view of a plasma separator to explain the principle of the present invention. The plasma separator was made using a bundle of semipermeable hollow fibers as shown in fig. 1, and a flow of the separated plasma was observed. In Fig. 1, in a container 1, were provided a blood flow inlet 2 and a blood flow outlet 3 at the both end thereof. A bundle of semipermeable hollow fibers 4 was provided in the container 1 to connect two blood rooms 5 and 6, which were provided at the insides of both ends of the container 1, respectively. The both ends of the bundle 4 were fixed to the container 1 with sealants 7 and open to the rooms 5 and 6, respectively.

When blood flowed into the container 1 through

the inlet 2 as in the direction of an arrow shown, the blood was separated into plasma and blood rich in blood cells in the bundle 4. The separated plasma flowed into a reservoir 8 sorrounded by two blood rooms 5 and 6, the container 1 and the bundle 4. In this context, the reservoir 8 was devided into three spaces with two partition plates 9 and spaces of the both ends were connected with a tube 10, whereby there was found a fact that the separated plasma flowed in the tube 10 at a considerable high speed and its flow was maintained even though a pressure drop within the tube 10 was raised.

The present invention makes use of such a fact, i.e. a reservoir in which the filtrated plasma flows is devided with porous partition plates to form a plasma treating room and in the treating room are charged a plasma treating agent, whereby the separated plasma can be purified by passing through the treating agent in the treating room on account of the flow of the plasma outside of the bundle of hollow fibers, and the purified plasma can be returned to the blood having a high concentration of blood cells.

In accordance with the present invention, there is provided an apparatus for purification of blood comprising:

a hollow container having a blood flow inlet and a blood flow outlet at the both ends thereof, respectively,

an impure blood room and a purified blood room coupled with said inlet and outlet, respectively, so that the blood can flow through them,

a bundle of hollow fibers made of semipermeable membrane connecting said impure blood room and said purified blood room so that the blood can flow through them, and

a treating room which is formed by deviding a space sorrounded by said hollow container, impure blood room and purified blood room with porous partition plates and said bundle of hollow fibers, and charged with a

plasma treating agent.

Fig. 1 is a schematic longitudinal sectional view of a plasma separator to explain the principle of the present invention; and

Fig. 2 and Fig. 3 are schematic longitudinal sectional views of the embodiments of the apparus for purification of blood of the present invention, respectively.

Hereinafter, an apparatus for purification of blood of the present invention is explained referring to the attached drawings showing an embodiment, respectively.

Fig. 2 shows an embodiment of the apparatus of the present invention in the longitudinal section, wherein the same numbers as in Fig. 1 represent the same members, respectively. Arrow heads in Fig. 2 show a flow of blood.

In Fig. 2, two porous partition plates 11 are provided in the container 1 to devide the reservoir, in which the plasma flows, into an impure plasma room 12, a plasma treating room 13 and a purified plasma room 14. In the plasma treating room 13 are charged plasma treating agents 15. The porous partition plate 11 is made of any materials as long as not the treating agent 15 but the plasma can pass through the plate.

Blood is introduced via blood flow inlet 2 into an impure blood room 5a by means of an external blood circulation pump (not shown) and is separated into blood having a high concentration of blood cells and plasma during passing through the bundle of hollow fibers 4 due to a flow inlet pressure.

At that time, a pressure difference corresponding to a pressure drop caused by the bundle of hollow fibers arises between the impure blood room 5a and the purified blood room 6a and also the blood pressure in the bundle of hollow fibers changes by a gradation that the blood pressure of a nearer point to the inlet 2 is higher.

When the treating agents are not charged in the plasma treating room 13, the pressure drop along the plasma flow scarcely arises and the pressure of the plasma is the middle between the pressure in the bundle near the inlet 2 and the pressure in the bundle near the outlet 3, if the plasma is in a closed structure and not taken out of the container. Therefore, in that case, the plasma flows back into the hollow fibers in the vicinity of the downstream side of the fibers because the pressure of the plasma is higher than that in the bundle near the outlet 3. In the conventional manner, the plasma pressure is maintained lower than that in the hollow fibers by taking out the plasma by means of pump.

On the contrary, in the apparatus of the present invention, since the plasma treating room 13 is charged with the treating agents, a suitable pressure drop arises in the flow of plasma so that pressure in the purified plasma room 14 is maintained larger than that in the hollow fibers of the corresponding portion while pressure in the impure plasma room 12 and in the plasma treating room 13 are maintained lower than those in the hollow fibers of the corresponding portions, respectively. As the results, the blood flowing in the container is separated into plasma and blood cells in the portions of the bundle of hollow fibers 4 corresponding to the impure plasma room 12 and the plasma treating room 13 and the separated plasma flows through the plasma treating room 13 toward the purified plasma room 14, whereby the objects to be removed are removed from the plasma by means of the plasma treating agents 15. The purified plasma returns back into the hollow fibers from the purified plasma room 14 and is mixed with the blood having a high concentration of blood cells, sent to the purified blood room 6a, and them, flows out from the outlet 3.

Sealant 7a on the side of the impure blood room 5a must be made from material through which both the blood cells and the plasma cannot pass, but sealant 7b on

the side of the purified blood room 6a may be made from the same material as that for the porous partition plates 11.

With respect to the charging of plasma treating agents, it is important to select its kind or charging density so that the pressure relationship between the respective portions becomes as mentioned above due to the pressure drop in the flow of plasma by charging. The plasma treating agent must be selected according to the objects to be removed from the blood. There can be used in the present invention, for instance, activated carbon, alumina, ion exchange resin, synthetic or half-synthetic adsorbent such as adsorbent made of a water-insoluble carrier holding matereals having affinity for the objects to be removed, and the like. Moreover, when the plasma treating agent containing immobilized enzymes is employed, the objects to be removed can be removed by a chemical reaction.

As the objects to be removed, there can be exemplified, for instance, waste products, LDL cholesterol, protein bound toxin, various causal objects of diseases related to innumity including an immune complex of an autoantibody, and the like.

The kind or charging density to be selected of the plasma treating agent is also varied according to flow rate of blood, kind and separatability of the semipermeable hollow fiber, permeation rate of plasma, charged amount of the treating agents, and the like, therefore, may be determined by integrating and considering all the requirements and the facts.

A porous hollow fiber usable in the present invention is a porous hollow fiber having a high plasma permeation rate, and in case of using such a fiber, a satisfactorily fast flow rate of plasma can be obtained. A porous hollow fiber having a diameter of pores at the inside surface of 0.01 to 10 μm, preferably 0.1 to 2 μm and a permeation rate for pure water not less than 2 $ml/m^2 \cdot min \cdot mmHg$, preferably of 50 $ml/m^2 \cdot min \cdot mmHg$ is

advantageously used. When the diameter of pores is not more than 0.01 μm, a permeation rate of the objects to be removed is small and a purification efficiency is remarkably lowered. On the contrary, when the diameter of pores is not less than 10 μm, a blood cell passes through the hollow fiber or blocks the pores of the hollow fiber. When the permeation rate for pure water is not more than 2 $ml/m^2 \cdot min \cdot mmHg$, too many hollow fibers are necessary in order to effectively purify blood, and as the result, the amount of blood and plasma outside a body is increased during the extracorporeal circulation.

According to the present invention, an inner diameter of the hollow fiber is suitably 250 to 500 μm and about 2,000 to 4,000 hollow fibers having such an inner diameter are preferably used in the form of a bunch.

The material for the hollow fiber is not limited to any specific materials, as long as it meets the above-mentioned requirements. Typical examples of such a material are, for instance, polysulfone, cellulose acetate, polypropyrene, polyethylene, polycarbonate, polyvinylalcohol, ethylene-vinylalcohol copolymer, polyacrylonitrile, polyamide, and the like.

Fig. 3 shows another enbodiment of the present invention, wherein the same numbers as in Fig. 2 represent the same members, respectively. An apparatus of Fig. 3 is the same as that of Fig. 2 except that the porous partion plates 11 are inclined and that the shape of the container 1 is different as shown.

As described above, the apparatus for purification of blood of the present invention is able to proceed the separation process of blood, the purification process of plasma and the mixing process of plasma with blood simultaneously by itself, while originally and conventionally those three processes have been proceeded in the separated three devices, respectively, and therefore, the pump for circulating plasma and the plasma path are eliminated from the apparatus. Further, in the

present invention, the purified blood can be obtained from the blood flow outlet by using only the pump for circulating blood outside a body, and moreover, complicated and troublesome operations required for controlling pressure during separation of blood can be largely reduced.

The present invention is more specifically described and explained by menas of the following Example. It is to be understood that the present invention is not limited to the Example, and various changes and modifications may be made in the invention without departing from the spirit and scope thereof.

Example 1

Using the apparatus as shown in Fig. 2, the waste products were removed from fresh cow blood.

In a container having a length of 23 cm and an outer diameter of 50 mm, was provided a bundle of hollow fibers consisting of 2,700 porous hollow fibers of polysulfone having an outer diameter of 400 μm, an inner diameter of 300 μm, a diameter of pores at the inside surface of 0.2 μm, a diameter of pores at the outside surface of 0.8 μm and a permeation rate for pure water of 500 $ml/m^2 \cdot min \cdot mmHg$, and the both ends of the bundle were fixed to the container with sealants of polyurethane, respectively. Two of the porous partion plates made of polycarbonate having a diameter of pores of 1 μm were provided in the container at the positions of 50 mm from the ends of the bundle of hollow fibers, respectively. 2,000 g of activated carbons having average particle size of 0.8 mm were charged between the porous partion plates.

Through the thus constructed apparatus, 4 ℓ of fresh cow blood was circulated and passed at a flowing rate of 100 ml/min. The blood which was obtained from the blood flow outlet had concentrations of uric acid and creatinine decreased by 58 % and 63 % in comparison with those in the blood at the blood flow inlet, respectively.

WHAT IS CLAIMED IS:

1. An apparatus for purification of blood comprising:

a hollow container having a blood flow inlet and a blood flow outlet at the both ends thereof, respectively,

an impure blood room and a purified blood room coupled with said inlet and outlet, respectively, so that the blood can flow through them,

a bundle of hollow fibers made of semipermeable membrane connecting said impure blood room and said purified blood room so that the blood can flow through them, and

a treating room which is formed by deviding a space sorrounded by said hollow container, impure blood room and purified blood room with porous partition plates and said bundle of hollow fibers, and charged with a plasma treating agent.

2. The apparatus of Claim 1, wherein a diameter of pores at the inside surface of said hollow fiber is 0.01 to 10 μm.

3. The apparatus of Claim 1, wherein siad hollow fiber has a permeation rate for pure water of not less than 2 $ml/m^2 \cdot min \cdot mmHg$.

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FIG. 1

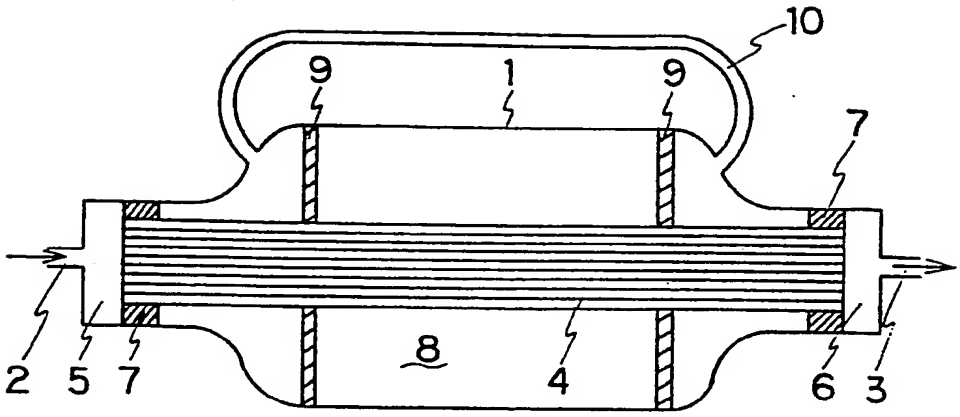


FIG. 2

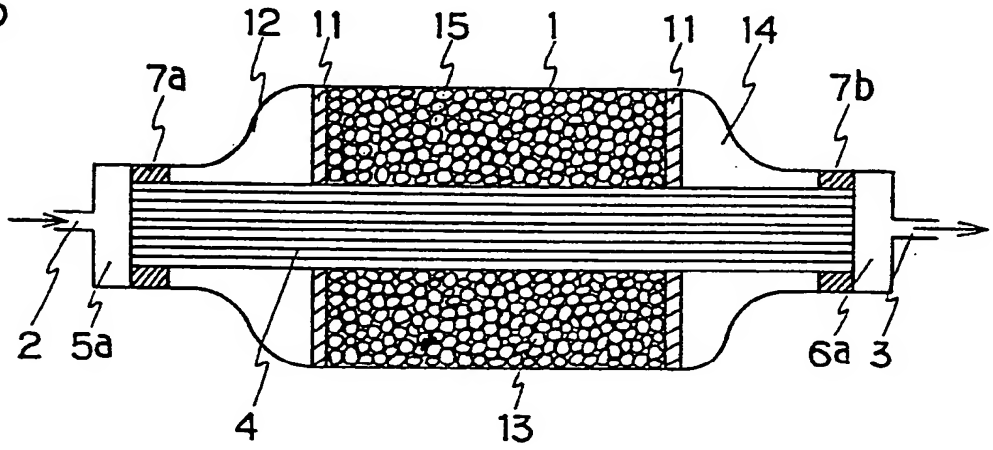
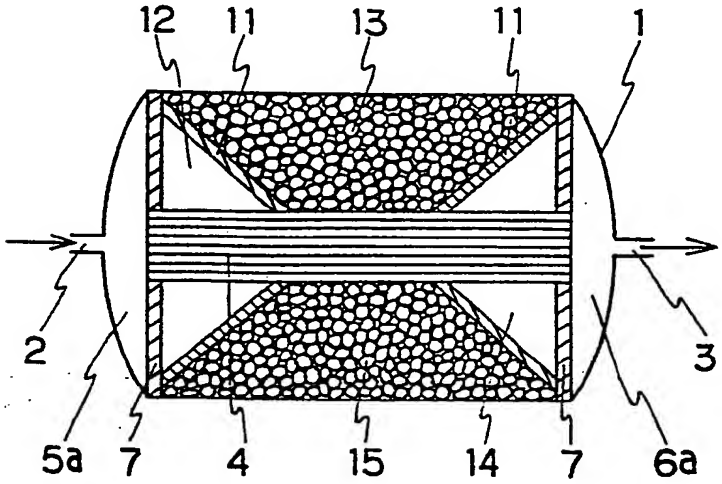


FIG. 3



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EUROPEAN SEARCH REPORT

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EP 84109703.3

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	FR - A1 - 2 510 412 (LAYME INV.) * Totality, especially fig. 2, page 4, line 30 - page 5, line 8 *	1	A 61 M 1/34 A 61 M 1/36
A	DE - A1 - 3 101 159 (U.R. SHETTIGAR) * Totality, especially pages 15, 20-25 *	1,2	
A	US - A - 4 243 532 (N. TSUDA et al.) * Totality *	1,2	
A	DD - A - 200 3118(CORDIS DOW CORP.) * Abstract; page 17, claim 1 *	1,3	TECHNICAL FIELDS SEARCHED (Int. Cl.4) A 61 M 1/00 B 01 D 13/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	28-01-1985	LUDWIG

CATEGORY OF CITED DOCUMENTS

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